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| 08/862,442 | 05/23/97 | SHYJAN | A 07334/004002 |

EXAMINER
HM22/0113
WORRALL, T

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DATE MAILED: 01/13/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

## OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 12/08/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) 29-50 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☐ Claim(s) _____ is/are rejected.
☒ Claim(s) 29-50 is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 7
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--



★ U.S. GPO: 1998-421-632/40206

## DETAILED ACTION

### *Priority*

1. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the parent application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for some claims of this application.

This application is a Divisional application of Application No. 08/623,679 filed April 16, 1996, which is a CIP of Application No. 08/412,431 (US Pat No: 5,412,431) filed March 29, 1995, and names the same inventor as the prior applications. The invention is drawn to a series of polypeptides encoded by polynucleotide sequences. Claims drawn to the polynucleotide sequence defined by SEQ ID NO:2 and the polypeptide sequence defined by SEQ ID NO:3 are enabled by Application 08/412,431 and have a priority date of March 29, 1995. Claims drawn to other sequences are not enabled by the original application, and have the April 16, 1996 priority date of Application 08/623,679. Accordingly, claims 31, 37, 40, and 45 have the March 29, 1995, priority date, and claims 29, 30, 32-36, 38, 39, 41-44, and 46-50 have the April 16, 1996, priority date.

### *Drawings*

2. New formal drawings are required in this application for the reasons cited in the attached Notice of Draftsperson's Patent Drawing Review. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the Patent and Trademark Office no longer prepares new drawings.

3. Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1 and 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a polypeptide comprising naturally occurring allelic variants of SEQ ID NOS:3, 7, and 9. The criteria for sequences that constitute a naturally occurring allelic variant, however, are indefinite. The metes and bounds for what comprises a naturally occurring allelic variant are undefined, particularly in the absence of any definition of which mutations would change the specific biochemical activity, as opposed to the tertiary structure, of the gene product.

6. Claims 43-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn polypeptides encoded by the nucleic acid sequences that hybridize under stringent conditions to SEQ ID NOS:2, 6, or 8, or the cDNA clones contained in NRRL Deposit No. B-21426, ATTC Accession No. 97880, or ATTC Accession No. 97881.

While the specification discusses the criteria for hybridization of different stringency and gives examples of hybridization conditions at those stringencies from page 44 line 22 to page 46 line 5, it does not specifically define the different stringencies as limited to the conditions presented in those examples. Further, while the terms "high stringency," "moderate stringency," and "low stringency" have examples in the specification, the term "stringency" itself is not defined. The claims are therefore indefinite, since the metes and bounds of nucleic acids hybridizing "under "stringent conditions" are not known.

7. Claims 30 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to "heterologous" amino acid sequences. "Heterologous" is a relative term that defines a sequence in terms of another sequence. The claim is therefore indefinite, since there is no point of reference to determine what constitutes a "heterologous" amino acid sequence.

8. Claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to a peptide "wehrein." Changing "wehrein" to "wherein" would obviate this rejection.

9. Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The claim is drawn to an "ellelic variant." The term "ellelic" is indefinite. Changing "ellelic" to "allelic" would obviate this rejection.

10. Claim 49 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to "cNDA." The term "cNDA" is indefinite. Changing "cNDA" to "cDNA" would obviate this rejection.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. The specification is objected to under 35 USC 112, first paragraph, and Claims 29 and 40-42 are rejected under 35 USC 112 first paragraph as failing to provide sufficient guidance to enable one skilled in the art to make polypeptides comprising naturally occurring allelic variants of the amino acid sequences of SEQ ID NO:3, 7, or 9.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims since the specification gives no guidance on or exemplification of how to make all of these types of modified proteins. The claims, as broadly written, read on amino acid sequences comprising naturally occurring allelic variants. However, applicant has not enabled all of these types of alleles because it has not been shown where the differences in the disclosed sequences

would be altered, or that these would result in a naturally occurring allele as opposed to a misfolded protein, truncated protein, etc.

The specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed protein can be tolerated that will allow the protein to retain functional properties. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (see Bowie et al (Science, 247:1306-1310, 1990, p. 1306, col.2). The specification and claims leave one skilled in the art to embark on experimentation of his own since no single allele has been disclosed or taught in the specification. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make every allele that will be correctly folded and functional as claimed. Therefore, in view of the speculative nature of the invention, the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

~~13.~~ Claims 29 and 40-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:3, 7, or 9 and therefore the written description is not commensurate in scope with the claims drawn to naturally occurring allelic sequence variants of a polynucleotide comprising the amino acid sequence consisting of SEQ ID NOS:3, 7, and 9.

*Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome, and differing from other alleles of that locus at one or more mutational sites ( page 17). Thus, the structures of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NOS:3, 7, and 9, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity

or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, in *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description... 'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Therefore only isolated polypeptides comprising amino acid sequences defined by SEQ ID NO:3, 7, or 9, but "naturally occurring allelic variants" of the polypeptides, meet the written description provision of 35 USC 112, first paragraph.

***Claim Rejections - 35 USC § 103***

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 43-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boeringer Mannheim 1991 Catalog (page 557) catalog in view of Zubay (Biochemistry, page 912, Adison-Wesley Publishing Company Inc. 1984). The claims are drawn polypeptides encoded by the nucleic acid sequences that hybridize under stringent conditions to SEQ ID NOS:2, 6, or 8, or the cDNA clones contained in NRRL Deposit No. B-21426, ATTC Accession No. 97880, or ATTC Accession No. 97881.

The Boeringer Mannheim Catalog teaches a library of every six base long ($(dN)_6$) nucleic acid primers (page 557, Primer, random $p(dN)_6$). Since the mixture comprises every permutation of a 6-mer polynucleotide sequence, several of the polynucleotide sequences can hybridize to the claimed sequences. The reference differs from the instant invention by not teaching that a polypeptide is encoded by the sequence.

Zubay et al teach that polypeptides are produced by encoded polynucleotide sequences.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to obtain any 2 amino acid polypeptide described by SEQ ID NO:3, 7, or 9 by using the polynucleotide sequence primers defined in the Boeringer Mannheim Catalog that hybridize to the nucleic acid sequences encoding SEQ ID NO:3, 7, or 9. One of ordinary skill in the art at the time the invention was made would have been motivated to produce the polypeptide encoded by specific nucleic acid sequences within the library since it is well known in the art that

polypeptide sequences are encoded by nucleic acid sequences. Further, since the degenerate set of nucleic acid sequences includes every permutation of 6 base polynucleotide, every sequence encoding 2 amino acid polypeptide within SEQ ID NO: 3, 7, and 9 would be present. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Conclusion***

16. CLAIMS 31-39 ARE ALLOWABLE, ABSENT DEPENDENCE ON CLAIM 29.

17. Any inquiry concerning the communication or earlier communications from the examiner should be directed to Timothy A. Worrall, Ph.D. whose telephone number is (703) 308-9348. The examiner can normally be reached on Monday through Friday from 8:30 A.M. to 5:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone number for this Group is (703) 305-3014.

Communications via Internet-e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [paula.hutzell@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that

sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements under 35 U.S.C.122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997, at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Timothy A. Worrall, Ph.D.

December 18, 1998

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER